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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,525	07/16/2004	Bart Staels	BJS-3665-106	8262

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,525	STAELS, BART	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-79* is/are pending in the application.

4a) Of the above claim(s) *59,60 and 79* is/are withdrawn from consideration.

5)☒ Claim(s) *43, 45-47, 53-58, 61 and 64-66* is/are allowed.

6)☒ Claim(s) *44,48-52 and 68-78* is/are rejected.

7)☒ Claim(s) *51,52,62 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 43-58 and 61-78, in the reply filed on 01/09/2007 is acknowledged.

2. Claim 59, 60, and 79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 01/09/2007.

3. Claims 43-58 and 61-78 are under consideration.

Information Disclosure Statement

4. The information disclosure statement filed 07/16/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has been considered only for references of which copies have been received. References not considered are indicated by strikethrough and considered references are indicated by examiner's initials on the signed IDS to be placed in the application file. Applicant need not provide duplicate copies of references entered into the record by the examiner on form PTO-892 in this office action.

Claim Objections

5. Claims 51 and 52 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are drawn to methods according to claim 43, wherein the REV-ERB ALPHA receptor comprises sequence SEQ ID NO: 4 or a fragment or functional variant thereof (claim 51) or wherein the recombinant nucleic acid comprises sequence SEQ ID NO: 3 or a fragment thereof. Claim 43 recites recombinant nucleic acid coding a REV-ERB ALPHA receptor. The specification teaches ([0024] of the published application), "The term "fragment" typically designates a polypeptide comprising from 5 to 200 consecutive amino acids of SEQ ID NO: 4, preferably from 5 to 150, even more preferably from 5 to 100. Particular examples of fragments are polypeptides of 5 to 80 amino acids. Preferably, the fragments comprise a functional domain of sequence SEQ ID NO: 4, for example a transcription inhibitor domain and/or a DNA binding domain." A fragment comprising only 5 consecutive amino acids or even a full functional domain would not be a REV-ERB ALPHA receptor. Likewise, a DNA fragment coding only a portion of the receptor would be outside of the scope of "coding a REV-ERB ALPHA receptor." Therefore, it would be possible to infringe claims 51 or 52 without infringing claim 43.

6. Claims 62 and 63 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are drawn to a cell according to claim 61, wherein the REV-ERB ALPHA receptor comprises sequence SEQ ID NO: 4 or a fragment or

functional variant thereof (claim 62) or wherein the recombinant nucleic acid comprises sequence SEQ ID NO: 3 or a fragment thereof (claim 63). Claim 61 recites recombinant nucleic acid coding a REV-ERB ALPHA receptor. It would be possible to infringe claims 62 or 63 without infringing claim 61 for reasons completely analogous to claims 51, 52, and 43 above.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 48-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 48 is drawn to a method according to claim 43, wherein the test compound is contacted with genetically modified pre-adipocyte cells in the presence of at least one activator of a gene involved in the adipocyte differentiation process. It is not clear how this claim alters or limits the method of claim 43. Claim 43 recites that, "adipocyte differentiation of said cells is measured or determined". It would appear, therefore, that "presence of at least one activator of a gene involved in the adipocyte differentiation process" is implicit and intrinsic to the method. Otherwise there would be no differentiation to measure. Even if the test compound were the only stimulator of differentiation in the method of claim 43, its presence would satisfy the limitations of claim 48.

9. Claim 49 is drawn to a method according to claim 43, wherein the test compound is contacted with genetically modified pre-adipocyte cells in the presence of at least one activator of the PPAR gamma gene. Claim 50 specifies that the activator of the PPAR gamma gene is

selected in the group of C/EBP beta, C/EBP delta and ADD1 (SREBP1c). Again it is not clear how these claims limit the method of claim 43. The cell recited in claim 43 is a pre-adipocyte, which intrinsically has at least one of the recited activators. The claims do not specify that the activators are overexpressed or otherwise different from the endogenous factors.

10. Claim 68-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 68 is drawn to a method for preparing a pre-adipocyte cell according to claim 61, wherein a recombinant nucleic acid coding a REV ERB ALPHA receptor is introduced into a pre-adipocyte cell. Claim 77 is drawn to a method according to claim 68, wherein the recombinant nucleic acid additionally comprises the sequence SEQ ID NO: 1 or a fragment thereof comprising the sequence SEQ ID NO: 2. Claims 68 and 77 therefore appear to recite two embodiments of a method, wherein only a recombinant nucleic acid coding a REV ERB ALPHA is required in the method of claim 68. However, claim 68 recites the cell of claim 61,which comprises a recombinant nucleic acid coding a REV-ERB ALPHA receptor, said recombinant nucleic acid further comprising sequence SEQ ID NO: 1 or a fragment thereof comprising sequence SEQ ID NO: 2. It does not seem likely that such a cell would be made in a method wherein nucleic acid coding a REV ERB ALPHA is added by itself, as implied by claim 68 in view of claim 77. The remaining claims are unclear as they depend from claim 68.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods employing genetically modified pre-adipocyte cells comprising a recombinant nucleic acid coding a REV-ERB ALPHA receptor, wherein the REV-ERB ALPHA receptor comprises sequence SEQ ID NO: 4 or wherein the recombinant nucleic acid comprises sequence SEQ ID NO: 3 does not reasonably provide enablement for methods employing unlimited fragments or variants of SEQ ID NO: 3 or SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re

Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The nature of the invention:* The claims are drawn to a methods for identifying compounds that modulate adipocyte differentiation, wherein (i) a test compound is contacted with a population of genetically modified pre-adipocyte cells comprising a recombinant nucleic acid coding a REV-ERB ALPHA receptor, wherein the REV-ERB ALPHA receptor comprises sequence SEQ ID NO: 4 or a fragment or functional variant thereof (claim 51) or wherein the recombinant nucleic acid comprises sequence SEQ ID NO: 3 or a fragment thereof.

Simply exposing preadipocytes to test agents under conditions that normally permit differentiation would serve to identify compounds that modulate adipocyte differentiation. The alleged novelty and advantage of the claimed method, therefore, is the potential for identifying those molecules capable of interacting either with the REV-ERB ALPHA receptor or with other receptors involved in the adipocyte differentiation program which are regulated with REV-ERB ALPHA receptors ([0013] in the published application). Therefore, the claimed method requires the presence of a form of REV-ERB ALPHA that has a measurable activity or effect.

b. *The breadth of the claims:* The specification teaches [0024], "The term "fragment" typically designates a polypeptide comprising from 5 to 200 consecutive

amino acids of SEQ ID NO: 4, preferably from 5 to 150, even more preferably from 5 to 100. Particular examples of fragments are polypeptides of 5 to 80 amino acids."

c. The state of the prior art and the predictability or lack thereof in the art: The prior art teaches that REV-ERB ALPHA is a transcriptional repressor that binds to a specific response element in DNA. By analogy to known nuclear receptors, the prior art provides guidance for the region of REV-ERB ALPHA likely to comprise a DNA binding domain. The prior art does not teach any functional domain or fragment comprising only 5 consecutive amino acids.

d. The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification teaches [0024], "Preferably, the fragments comprise a functional domain of sequence SEQ ID NO: 4, for example a transcription inhibitor domain and/or a DNA binding domain." The boundaries of these preferred domains are not provided. The tolerance of these domains to sequence variation is not known. The entire cDNA encoding the REV-ERB ALPHA receptor was used in all of the disclosed examples wherein the any recombinant nucleic acid was introduced into pre-adipocytes.

e. The quantity of experimentation needed: As the number of potential fragments and variants is large and likely to include numerous inoperative embodiments, it would require undue experimentation for one of skill in the art to make and use the claimed invention in its full scope.

13. Claims 44, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The fact that a patent is directed to method entailing use of a compound, rather than to the compound *per se*, does not remove patentee's obligation to provide description of the compound sufficient to distinguish infringing methods from noninfringing methods (University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004)). In this case, claim 44 is drawn to methods that comprise administration of a genus of compounds recited as "activator of a receptor involved in the adipocyte differentiation process". Claim 48 can be construed as being drawn to methods that comprise administration of a genus of compounds recited as "gene involved in the adipocyte differentiation process". Claim 49 recites "activator of the PPAR gamma gene", which is a subgenus of the genus recited in claim 48. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a general functional characteristic of being an activator of a receptor or a gene involved in the adipocyte differentiation process. Thus, each genus is defined entirely by what it is supposed to do, not by what it is. The art recognizes certain receptors and certain activators thereof as being involved in adipocyte differentiation; these are recited in claims 45-47, for example. The art recognizes that

certain gene products activate the PPARgamma gene; these are recited in claim 50, for example. The specification teaches, however, that adipocyte differentiation is a complex process the molecular components of which are *becoming* more clearly understood [0004] (emphasis added). The sizes of the genera of receptors and genes involved is not known and is unlimited, as there is no definition as the degree of "involvement" a receptor or gene must have in order to be included. As the receptors and genes are not described, then certainly the genus of activators, unlimited to any chemical class, is not described. The genus of activators is still indeterminably large even when only one gene is considered, as in claim 49. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

14. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

15. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

16. Claim 51 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The fact that a patent is directed to method entailing use of a compound, rather than to the compound *per se*, does not remove patentee's obligation to provide description of the compound sufficient to distinguish infringing methods from noninfringing methods (University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004)). In this case, the claims are drawn to methods that comprise administration of a genus of compounds recited as "REV-ERB ALPHA receptor comprises sequence SEQ ID NO: 4 or a fragment or functional variant thereof". To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. According to the specification, "The term "functional variant" encompasses natural variants, particularly those resulting from polymorphism(s), splicing(s), interspecies variation(s), and the like. Said term also includes synthetic variants, particularly polypeptides comprising a sequence derived from sequence SEQ ID NO: 4 by one or more mutations, deletions, substitutions and/or additions of one or more residues. In a preferred manner, a synthetic variant shows 75% primary sequence homology with sequence SEQ ID NO: 4, even more preferably, at least 85%. The fragments or variants may further contain added

heterologous regions or chemical, enzymatic, immunologic, modifications, etc. For instance, said modifications may facilitate the production or purification of the receptor, improve its stability, increase its activity, etc." Therefore, although the term "functional" is used, the only factor present in the supporting definition is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

17. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

18. With the exception of SEQ ID NO: 4, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

19. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

20. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

21. Claims 44, 48-52, and 68-78 are rejected.

22. Claims 51, 52, 62, and 63 are objected to.

23. Claims 43, 45-47, 53-58, 61 and 64-66 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
12 April 2007

DAVID S. ROMEO
PRIMARY EXAMINER